GEORGIA INSTITUTE OF TECHNOLOGY OFFICE OF CONTRACT ADMINISTRATION

PROJECT ADMINISTRATION DATA SHEET

[X] ORIGINAL [ ] REVISION NO. _____

Project No./(Center No.) G-33-698 (R6291-0A0) GTRC/~~GIT~~ DATE 4 / 7 / 87

Project Director: P.G. McDougal School/~~Dept~~ Chemistry

Sponsor: National Science Foundation

Agreement No.: Grant No. CHE-8612735

Award Period: From 1/1/87 To 6/30/89* (Performance) 9/30/88 Reports

Sponsor Amount:	New With This Change	Total to Date
Contract Value: $		$ 171,000**
Funded: $		$ 65,000

Cost Sharing No./(Center No.) G-33-325 (F6291-0A0) Cost Sharing: $ 2,456

Title: Selective Deprotonation in Acrylic Systems

ADMINISTRATIVE DATA OCA Contact John B. Schonk x4-4820

1) Sponsor Technical Contact:

John S. Showell
National Science Foundation
MPS/CHE
Washington, DC 20550

202/357-7501

2) Sponsor Issuing Office:

Shirley P. Greene
National Science Foundation
DGC/MPS
Washington, DC 20550

202/357-9843

Military Security Classification: _____
(or) Company/Industrial Proprietary: _____

ONR Resident Rep. is ACO: _____ Yes _____ No
Defense Priority Rating: _____

RESTRICTIONS

See Attached NSF Supplemental Information Sheet for Additional Requirements.

Travel: Foreign travel must have prior approval — Contact OCA in each case. Domestic travel requires sponsor approval where total will exceed greater of $500 or 125% of approved proposal budget category.

Equipment: Title vests with GIT

COMMENTS:

*Includes a 6 month unfunded flexibility period
**Funding is expected for an additional 2 years

SPONSOR'S I.D. NO. 02,107,000,86,107

COPIES TO:

Project Director
Research Administrative Network
Research Property Management
Accounting
Procurement/GTRI Supply Services
Research Security Services
Contract Support Div.(OCA)(2) 1 Cat
Research Communications
GTRC
Library
Project File
Other _____

GEORGIA INSTITUTE OF TECHNOLOGY
OFFICE OF CONTRACT ADMINISTRATION

NOTICE OF PROJECT CLOSEOUT

Closeout Notice Date 09/04/91

Project No. G-33-698_____ Center No. R6291-0A0_____

Project Director MCDOUGAL P G_____ School/Lab CHEMISTRY_____

Sponsor NATL SCIENCE FOUNDATION/GENERAL_____

Contract/Grant No. CHE-8612735_____ Contract Entity GTRC

Prime Contract No. _____

Title SELECTIVE DEPROTONATION IN ACYCLIC SYSTEMS_____

Effective Completion Date 900630 (Performance) 900930 (Reports)

Closeout Actions Required:	Y/N	Date Submitted
Final Invoice or Copy of Final Invoice	N	_____
Final Report of Inventions and/or Subcontracts	Y	910715
Government Property Inventory & Related Certificate	N	_____
Classified Material Certificate	N	_____
Release and Assignment	N	_____
Other _____	N	_____

CommentsINVOICING VIS LINE-OF-CREDIT. 98A SATISFIES PATENT REPORTING REQUIREMENT._____

Subproject Under Main Project No. _____

Continues Project No. _____

Distribution Required:

Project Director	Y
Administrative Network Representative	Y
GTRI Accounting/Grants and Contracts	Y
Procurement/Supply Services	Y
Research Property Managment	Y
Research Security Services	N
Reports Coordinator (OCA)	Y
GTRC	Y
Project File	Y
Other _____	N
_____	N

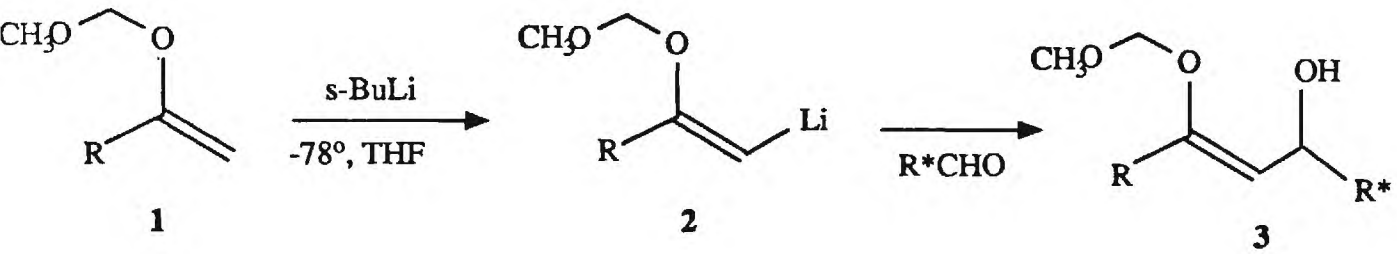
NOTE: ~~Final Patent Questionnaire sent to PDPI.~~ apr

Technical Progress Report
NSF Grant **CHE-8612735**

Principal Investigator: **Patrick G. McDougal**
School of Chemistry
Georgia Institute of Technology
Atlanta, GA 30332

A. Directed Lithiations of Enol Ethers:

In completing his Ph.D thesis, **Joseph G. Rico,** discovered that the direct β-lithiation of methoxymethyl(MOM) enol ethers is a general reaction. Listed below are examples in which β-lithiation is effectively acheived. We were most gratified that the presence of allylic protons (**4**) and/or additional oxygens (**6** and **7**) did not inhibit successful lithiation. As illustrated in structure **3** the power of this methodology lies in the exclusive formation of *Z*-olefins. Having defined the scope and limitations of this reaction, we are planning to explore the chemistry of the highly substituted



1 **2** **3**

4 R=octyl 70%
5 R=t-butyl 78%
6 R=$(CH_3)_2C$- 90%
OCH_3

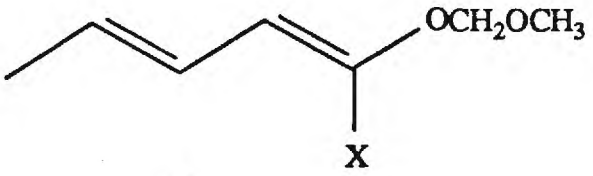
7 R=CH_3CH- 84%
OCH_2OCH_3
8 R=i-PrCH=CH- 70%

enol ethers (i.e. **3**) which result. A full paper describing the results to date is in preparation.

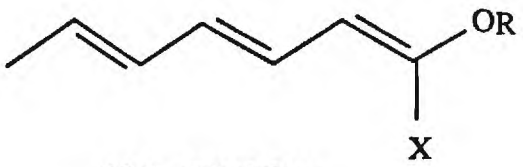
In addition to directing β-lithiation the MOM group is equally adept at directing α-lithiation. For example the MOM-diene **9** (X=H) and MOM-triene **10** (X=H) both undergo clean α-lithiation (X=Li) as evidenced by the formation of the corresponding silylated derivatives (X=$Si(CH_3)_3$). Furthermore the importance of the MOM group in effecting deprotonation was demonstrated by the inability to deprotonate the methoxy triene **11** (X=H). As we had originally hypothesized, we believe the second oxygen in the MOM group is effectively chelating to the organolithium bases thereby directing the deprotonation. This work has recently appeared as a communication in JOC (**J. Org. Chem.** *1987*,**52**,4817.)

B. Asymmetric Diels-Alder Reactions:

We had recently published (**J. Org. Chem.** *1986*,**51**,4492) that the asymmetric diene **12** undergoes a face selective Diels-Alder reaction. As the diene was synthesized via the β-lithiation



9

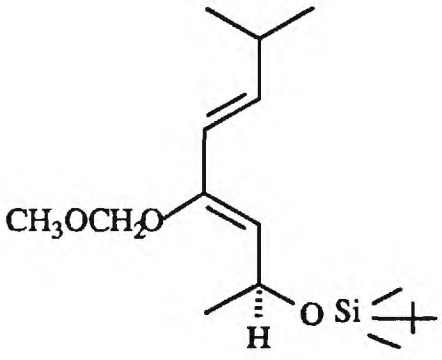


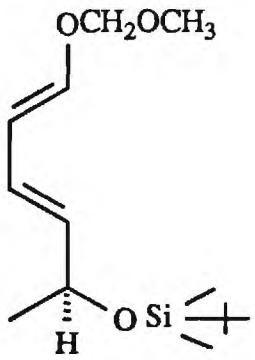
10 R=CH_2OCH_3

11 R=CH_3

methodology discussed above, this work was initially an outgrowth of our directed lithiation project. Due to the continued interest in asymmetric synthesis we have begun to explore this reaction in its own right. We reasoned that the increased face selectivity observed with **12** relative to related dienes was due to the presence of the alkoxy-substituent. This group had a dual effect. First, it

12



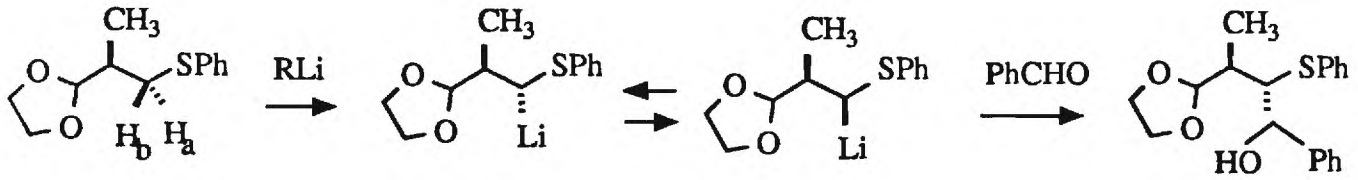


13

effected the conformational preferences of the asymmetric allylic carbon which in turn influenced the asymmetric induction. Second, it distorted the molecular orbitals of the diene so as to cant the transition state of the Diels-Alder reaction toward the asymmetric center thereby increasing the asymmetric induction. In order to separate these two effects we synthesized diene **13** starting from *S*-lactate. The synthesis of this material was accomplished with our recently reported methodology for the preparation of *Z,Z*-1-alkoxy dienes (**J. Org. Chem.** *1987*,**52**,4817). As with diene **12**, the chiral diene **13** showed complete face selectivity in its reaction with N-phenylmaleimide. Therefore the alkoxy substituent need not be placed so as to sterically effect the conformational preference of the chiral carbon. Due to the synthetic potential of these asymmetric Diels-Alder reaction we are probing the face selectivity of diene **13** with other dienophiles. This work is presently being carried out by a second year graduate student, **Joseph Jump**.

C. Acyclic Asymmetric α-Lithiated Sulides:

One aspect of my original proposal dealt with the diastereo- selective replacement of a hydrogen with a C-C bond (**14→16**). In the final product two new asymmetric centers are created and so one must be concerned about 1,2 and 1,3 asymmetric induction. Critical to the analysis of these inductions is the production, conformational stability, and fate of the intermediate organolithium **15**. In order to probe these factors we have generated the anion via deprotonation, Sn/Li exchange and reductive desulfenylation. In each instance a different ratio of organolithium diastereomers **15α** and **15β** should be produced initially. From analyzing the stereochemistry of the products produced upon quenching the organolithium with trimethylsilyl chloride we could track the fate of the



14 **15α** **15β** **16α β-OH** **16β α-OH**

intermediate organolithium **15**. From these studies we have concluded the following: (1) that at -78° the equilibration between the two diastereomers **15α** and **15β** is rapid; (2) that the ratio of silylated products reflects the equilibrium ratio of organolithiums; (3) the thermodynamic equilibrium favors **15α** to the tune of 97:3 (±1). This is to our knowledge the first study on the dynamics of α-lithiated sulfides (see the attached publication for details).

Particularly intriguing is the thermodynamic preference (2.3 kcal/mol) for diastereomer **15α**. While at present we have no good rationalization for this preference, we suspect that internal coordination of the lithium to the dioxolane ring is an important element in determining selectivity. We are exploring this point by creating other acylic α-lithiated sulfides and determining their diastereoselectivity. In addition we are attempting to improve the 1,3-stereoselectivity (see structure **16**) in the reaction of aldehydes with our lithiated sulfides. Toward this goal we have manipulated a number of factors including substituting SPh with other SR groups (R=o-methoxyphenyl,t-Bu), changing to more and less polar solvent systems and switching metals from Li to Cu,Al,Ti and Zn. Our preliminary results indicate that Li is the preferred metal, o-methoxyphenyl sulfide is the best SR group and pentane is the best solvent. That the presence of a chelating group in the sulfide influences stereoselectivity again raises the issue as to the exact role played by heteroatom coordination both before and after deprotonation. This work is presently being carried out by a third year graduate student **Brian Condon.**

Expenditures and Encumbrances as of 12/31/87

(see attached sheets)

From a total of $44,416.00 budgeted for direct costs there was, as of 12/31/87, a free balance of $13,110.00 (see attached sheet). This number should be approximately $18,500 due to an improper personal services encumbrance which is presently being corrected. This free balance exists due to my believe that the expiration date was 6/30/88 as listed on our internal account sheets. The outstanding capital outlay is presently being committed to an 8 kbar pressure reactor and will be encumbered in the near future. Materials and supplies is also expected to be zeroed by 6/30/88 as we anticipate several large purchases including reverse phase LC columns and flash chromatography silica gel.

The personal that were supported on this grant include:

Patrick G. McDougal (PI) $6,6063.00 - less than 2 months summer salary

Brian D. Condon $11,199.96 - full year RA

Joseph Jump $1347.39 - partial RA summer quarter

Proposed Budget 1/1/88-12/31/88

A proposed budget for $53,000 in total costs is attached. We have requested that 1.25 graduate students be funded as RA's ($11,500/year). The 0.25 RA would support a graduate student during the summer quarter.

Active and Pending Grants and Contracts

(1) National Science Foundation, "Selective Deprotonation in Acylic Systems", 1/1/87-12/31/89, $171,000 (this grant).

(2) National Institutes of Health, "Diels-Alder Reaction of Asymmetric Alkoxy Polyenes", 3 years, $230,567 (under review).

(3) National Cancer Institute, "The Synthesis of Congeners and Prodrugs of Anti-AIDS Compounds", 3 years, $435,784, as co-investigator on a contract (final review)

Publications Acknowledging NSF Grant

(1) McDougal,P.G.; Rico,J.G. "Stereoselective Synthesis and α-Lithiation of Alkoxy Polyenes" **J. Org. Chem.** *1987*,**52**,4819.

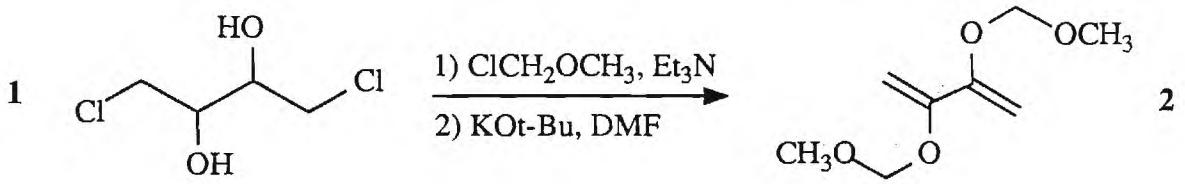
(2) McDougal,P.G.; Condon,B.D.; Lafosse,M.D.,Jr.; Lauro,A.M.; VanDerveer,D. "Diastereoselective Reactions of an Acyclic α-Lithiated Sulfide: A Case of Thermodynamic Control" **Tetrahedron Letters**, submitted for publication.

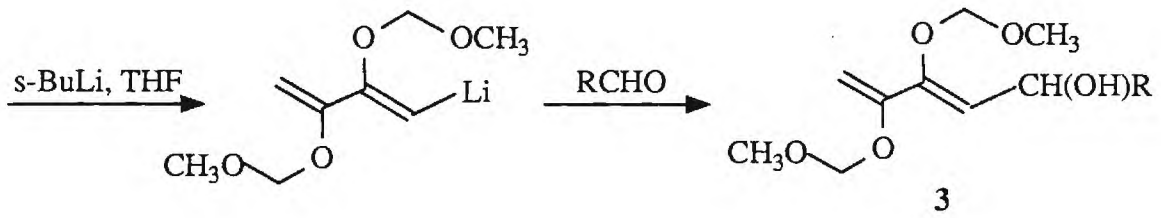
Technical Progress Report (1/88-1/89)
NSF Grant **CHE-8612735**

Principal Investigator: **Patrick G. McDougal**
School of Chemistry
Georgia Institute of Technology
Atlanta, GA 30332

A. Directed Lithiations of Enol Ethers:

The first stage of work on the directed β-lithiation of methoxymethyl enol ethers has been completed and has been submitted to the *Journal of the American Chemical Society* as a full paper (see enclosed preprint). Since our last progress report we have added a number of examples the most significant of which is the 2,3-dialkoxydiene **2**. This diene is readily available from the commercially available diol **1** and should provide us with a series of asymmetric alkoxy dienes for use in our continuing studies on the asymmetric Diels-Alder reaction (see section B). A new graduate student, **John Kerrigan**, has picked up this project



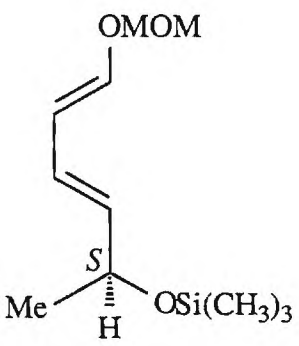


and is involved in studying the chemistry of the substitued enol ethers (such as compound **3**) which result from the β-lithiation reaction.

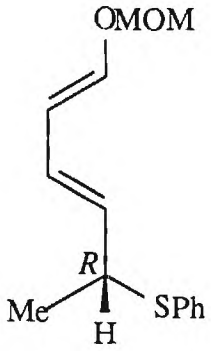
B. Asymmetric Diels-Alder Reactions:

Over the last year we have synthesized the three asymmetric dienes **4**, **5** and **6** according to our previously reported methodology (***J. Org. Chem.* 1987, *52*, 4817**). All of these dienes originate from chiral, nonracemic materials and hence are themselves nonracemic. The facial selectivity of these dienes is probed with with three dienophiles: N-phenylmaleimide (**7**), benzoquinone (**8**) and 4-phenyl-1,2,4- triazoline-3,5-dione (**9**). This is done since it has been established that the facial selectivity of asymmetric dienes is highly dependent on the nature of the dienophile. From this study several conclusions can be reached: (1) in accord with previous results (Tripathy and Franck *JACS* **1988**, *110*, 3257) the facial selectivity becomes increasingly *ul* selective as one procedes from N-phenylmaleimide (**7**) through benzoquinone (**8**) to the azadione (**9**); (2) in all cases the replacement of a 1-methyl group (see Tripathy and Frack) with a 1-alkoxy group (MOM) increases the *lk* selectivity; (3) a sulfur atom at the allylic position is more *ul* directing than an oxygen atom. The latter observation is in accord with the facial selectivity observed in the Diels-Alder reaction of substituted cyclopentadienes (Macauley and Fallis *JACS* **1988**, *110*, 4074).

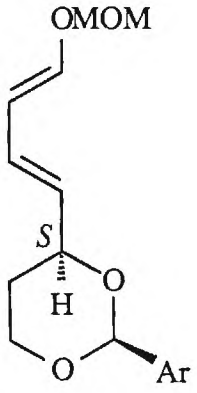
TABLE 1: Facial Selectivity of Asymmetric Dienes 4, 5 and 6.



4



5



6 Ar = 2,4,6-trimethylphenyl

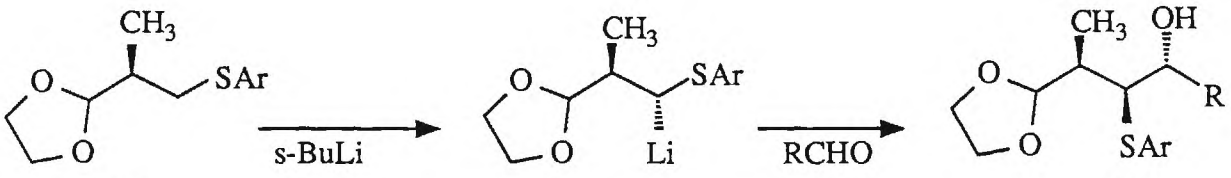
FACIAL SELECTIVITY WITH DIENOPHILES 7, 8 AND 9

	Diene 4	Diene 5	Diene 6
7	lk:ul >20:1	lk:ul 1.5:1	
8	lk:ul 3:1	lk:ul 1:1.2	lk:ul 3:1
9	lk:ul 1:1.1	lk:ul 1:4	

We have briefly explored the effect of Lewis acid on the facial selectivity of the benzoquinone (**8**) addition to diene **4** and found that both BF_3•Et_2O and $ZrCl_4$ gave more of the *ul* stereoisomer resulting in a nearly 1:1 mixture of stereoisomers. This work is presently being written up as a communication to *Tetrahedron Letters*. The student on this project, **Joe Jump**, is presently exploring the effect of pressure on facial selectivity. We would soon like to target some natural products using this methodology.

C. Acyclic Asymmetric α-Lithiated Sulfides:

Our studies have continued on the control of acyclic stereochemistry via the use of asymmetric organometallics. Our paper dealing with the selective formation of the



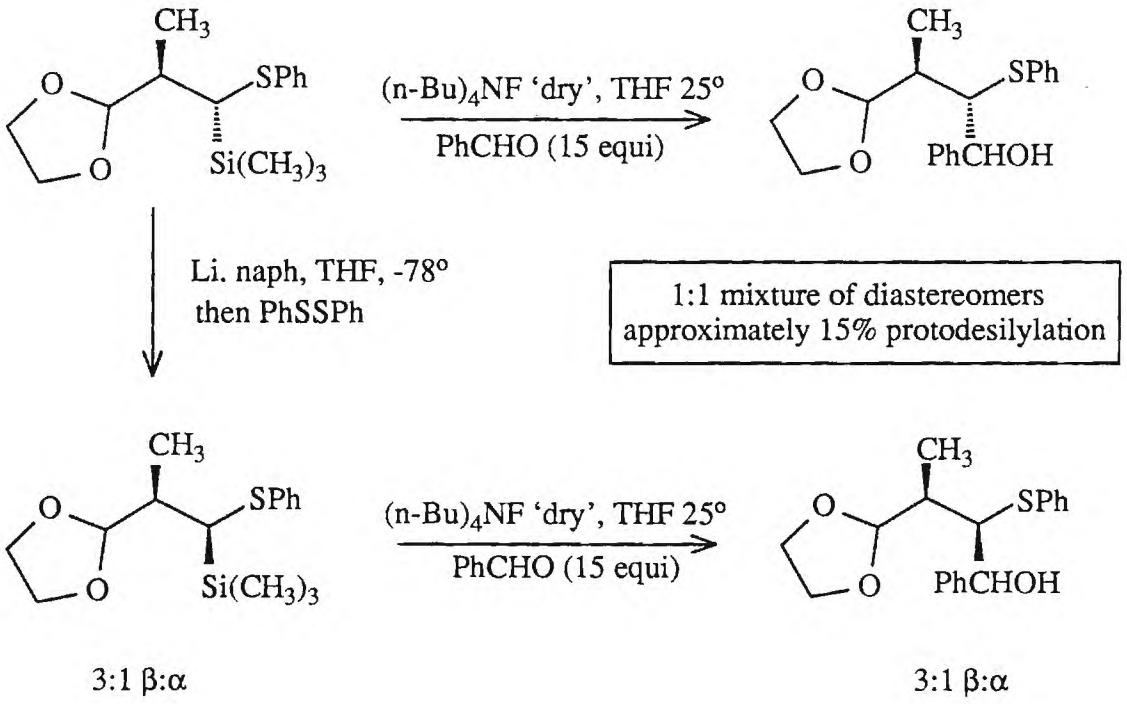
10 **11** **12**

a Ar = phenyl; **b** Ar = *o*-methoxyphenyl; **c** Ar = *o*-t-butylphenyl

asymmetric organolithium **11** has recently appeared in *Tetrahedron Letters* (enclosed are two reprints). Having an efficient preparation of the asymmetric organolithium **11** we have more recently concentrated on controlling the stereoselectivity of its reaction with aldehydes. This

has proven to be a much more difficult problem. However we have recently observed that incorporating steric bulk into the sulfide moiety has increased stereoselectivity significantly. For example treatment of the *o*-t-butylsulfide **10c** with s-BuLi (-78°, THF) followed by the addition of benzaldehyde yields **12c** in greater than 90% diastereomeric excess. The graduate student on this problem, **Brian Condon**, is now exploring the generality of this procedure.

As part of this project we were able to explore the stereochemistry of desilylative hydroxyalkylation. As shown below we have found that this reaction goes with retention of configuration. Besides giving us another handle for the control of acyclic stereochemistry, this result should be extremely useful to the synthetic community given the current interest in organosilicon chemistry. We have submitted a communication to *Tetrahedron Letters* outlining this result.



D. Publications Acknowledging NSF Grant:

(1) McDougal, P. G.; Rico J. G.: Stereoselective Synthesis and α-Lithiation of Alkoxy Polyenes. *J. Org. Chem.* ***1987***, *52*, 4817.

(2) McDougal, P. G.; Condon, B. D.; Lafosse, M. D.; Lauro, A. M.; VanDerveer, D.: Diastereoselective Reactions of an Acyclic α-Lithiated Sulfide: A Case of Thermodynamic Control. *Tetrahedron Letters* **1988**, *29*, 2547.

(3) McDougal, P. G.; Condon, B.D.: Retention of Configuration in the Desilylative Hydroxyalkylation of α-Silyl Sulfides. *Tetrahedron Lett.* submitted for publication.

(4) McDougal, P. G.; Rico, J. G.; Condon, B. D.; Kerrigan, J. E.: Direct β-Lithiation of Methoxymethyl Enol Ethers. *J. Amer. Chem. Soc.* submitted for publication.

Expenditures and Encumbrances as of 11/14/88

Budgeted Total Direct Costs (1st & 2nd years): $77,541.00

Free Direct Balance: $8,584.10

Majority of the unencumbered money ($7,208.89) resides in 'operating supplies and expenses'. It is anticipated that a surplus of some $3,000 will remain at the anniversity of this grant (1/1/89) and consequently our new budget has requested a shifting of some money to personnel services for the support of another 0.25 graduate stipend. We have recently received shipment of a high pressure reactor (8 kbar) which accounted for all our equipment money.

The personnel supported on this grant for the last year (1/1/88-12/31/88) are as follows:

Patrick G. McDougal (PI) $2346.85 - 0.6 month salary
-the rest of my summer salary was used to support graduate and undergraduate RA's (see below)
Brian D. Condon $8,399.97 - 9 month graduate RA
Joseph Jump $5599.98 - 6 month graduate RA
John Kerrigan $2799.99 - 3 month graduate RA
Marion Alexander $1394.00 - summer undergraduate RA

Proposed Budget 1/1/88-12/31/88

A proposed 3rd year budget for $53,000 in total costs is attached. We have requested that 1.5 graduate students be funded as RA's ($11,500.00/year). This represents an increase of 0.25 RA which would allow me to support three graduate students in the summer quarter. The requested increase in the personnel services budget comes at the expense of material and supplies. A slight carry over of supplies money from the 2nd year budget assures that we will have enough resources in this area.

Active Support

(1) National Sciece Foundation, "Selective Deprotonation in Acyclic Systems", 1/1/87-12/31/89, $171,000 (this grant)

(2) National Institutes of Health, "The Synthesis of Congeners and Prodrugs of Anti-AIDS Compounds", co-investigator (PI- Professor Leon Zalkow), 8/1/88-7/31/91, $648,000.

3rd Year
SUMMARY
PROPOSAL BUDGET

OMB No. 3145-0058
Exp. Date 12/31/85

FOR NSF USE ONLY		
PROPOSAL NO.	DURATION (MONTHS) Proposed	Granted
AWARD NO.		

ORGANIZATION
GEORGIA TECH RESEARCH CORPORATION

PRINCIPAL INVESTIGATOR/PROJECT DIRECTOR
Patrick G. McDougal

A. SENIOR PERSONNEL: PI/PD, Co-PI's, Faculty and Other Senior Associates (List each separately with title; A.6. show number in brackets)	NSF FUNDED PERSON-MOS. CAL.	ACAD	SUMR	FUNDS REQUESTED BY PROPOSER	FUNDS GRANTED BY NSF (IF DIFFERENT)
1. Patrick G. McDougal			2	$ 8,355	$
2.					
3.					
4.					
5. ( ) OTHERS (LIST INDIVIDUALLY ON BUDGET EXPLANATION PAGE)					
6. (1) TOTAL SENIOR PERSONNEL (1-5)			2	8,355	
B. OTHER PERSONNEL (SHOW NUMBERS IN BRACKETS)					
1. ( ) POST DOCTORAL ASSOCIATES					
2. ( ) OTHER PROFESSIONALS (TECHNICIAN, PROGRAMMER, ETC.)					
3. ( ) GRADUATE STUDENTS (1.5)				17,250	
4. ( ) UNDERGRADUATE STUDENTS					
5. ( ) SECRETARIAL-CLERICAL					
6. ( ) OTHER					
TOTAL SALARIES AND WAGES (A+B)				25,605	
C. FRINGE BENEFITS (IF CHARGED AS DIRECT COSTS) 25.5%				2,130	
TOTAL SALARIES, WAGES AND FRINGE BENEFITS (A+B+C)					
D. PERMANENT EQUIPMENT (LIST ITEM AND DOLLAR AMOUNT FOR EACH ITEM EXCEEDING $1,000.)					
TOTAL PERMANENT EQUIPMENT					
E. TRAVEL 1. DOMESTIC (INCL. CANADA AND U.S. POSSESSIONS)				1,000	
2. FOREIGN					
F. PARTICIPANT SUPPORT COSTS					
1. STIPENDS $					
2. TRAVEL					
3. SUBSISTENCE					
4. OTHER					
TOTAL PARTICIPANT COSTS					
G. OTHER DIRECT COSTS					
1. MATERIALS AND SUPPLIES				4,065	
2. PUBLICATION COSTS/PAGE CHARGES				325	
3. CONSULTANT SERVICES					
4. COMPUTER (ADPE) SERVICES					
5. SUBCONTRACTS					
6. OTHER					
TOTAL OTHER DIRECT COSTS					
H. TOTAL DIRECT COSTS (A THROUGH G)				33,125	
I. INDIRECT COSTS (SPECIFY) 60.0% of Total Direct Costs				19,875	
TOTAL INDIRECT COSTS					
J. TOTAL DIRECT AND INDIRECT COSTS (H + I)				53,000	
K. RESIDUAL FUNDS (IF FOR FURTHER SUPPORT OF CURRENT PROJECTS GPM 252 AND 253)					
L. AMOUNT OF THIS REQUEST (J) OR (J MINUS K)				$ 53,000	$

PI/PD TYPED NAME & SIGNATURE*	DATE	FOR NSF USE ONLY
Patrick G. McDougal	11/15/88	INDIRECT COST RATE VERIFICATION
INST. REP. TYPED NAME & SIGNATURE*	DATE	Date Checked / Date of Rate Sheet / Initials - DGC / Program

REED COLLEGE *Portland, Oregon 97202-8199*

CHEMISTRY
DEPARTMENT

July 15, 1991

Milton Stombler
College of Science
Georgia Institute of Technology
Atlanta, GA 30332

Dear Mr. Stombler:

Please find enclosed a copy of my final technical report and Form 98A for my NSF grant. I have also forwarded all the enclosed items directly to the project sponsor. I apologize for the delay in getting these materials to you. I trust this terminates my NSF grant.

Sincerely,

Patrick G. McDougal
Associate Professor of Chemistry

633-60
1,1

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NATIONAL SCIENCE FOUNDATION
Washington, D.C. 20550

FINAL PROJECT REPORT
NSF FORM 98A

PLEASE READ INSTRUCTIONS ON REVERSE BEFORE COMPLETING

PART I—PROJECT IDENTIFICATION INFORMATION

1. Institution and Address	2. NSF Program	3. NSF Award Number
Department of Chemistry Georgia Institute of Technology Atlanta, GA 30332	CHEM- Organic Synthesis	CHE-8612735
	4. Award Period From 1/1/87 To 6/30/90	5. Cumulative Award Amount $171,000

6. Project Title

Selective Deprotonation in Acyclic Systems

PART II—SUMMARY OF COMPLETED PROJECT *(FOR PUBLIC USE)*

The construction of carbon-carbon bonds remains a key challenge in the construction of new organic materials. As target molecules become more sophisticated it is imperitive that the bond forming methods become more efficient and selective. The work completed during this granting period involved the selective formation of carbon-carbon bonds via the selective deprotonation of weakly acidic carbon acids. In general the systems were acyclic and contained suitably placed heteroatoms which were used to direct the desired deprotonation. In this way a number of new and interesting organolithium reagents were developed. These included: (1) α- and β-lithiated enol ethers and dienyl ethers; (2) lithiated chiral, non-racemic enol ethers; and (3) chiral lithiated sulfides.

Once generated the above organolithiums were reacted with various carbon electrophiles to produce new carbon-carbon bonds. Majority of these reactions generated one or more chiral centers and in all these cases the degree of stereoselectivity was carefully monitored. Many of the above reagents proved to be highly stereoselectivty and hence a number of new methods for the construction of chiral carbon atoms were discovered. The synthetic methods developed during the course of this project should find use in the preparation of pharmaceuticals and other fine chemicals.

PART III—TECHNICAL INFORMATION *(FOR PROGRAM MANAGEMENT USES)*

1. ITEM *(Check appropriate blocks)*	NONE	ATTACHED	PREVIOUSLY FURNISHED	TO BE FURNISHED SEPARATELY TO PROGRAM	
				Check (✓)	Approx. Date
a. Abstracts of Theses		X			
b. Publication Citations		X			
c. Data on Scientific Collaborators		X			
d. Information on Inventions	X				
e. Technical Description of Project and Results		X			
f. Other *(specify)*					

2. Principal Investigator/Project Director Name *(Typed)*	3. Principal Investigator/Project Director Signature	4. Date
Patrick G. McDougal		7/15/91

PART IV - SUMMARY DATA ON PROJECT PERSONNEL

NSF Division CHEMISTRY- Organic Synthesis

The data requested below will be used to develop a statistical profile on the personnel supported through NSF grants. The information on this part is solicited under the authority of the National Science Foundation Act of 1950, as amended. All information provided will be treated as confidential and will be safeguarded in accordance with the provisions of the Privacy Act of 1974. NSF requires that a single copy of this part be submitted with each Final Project Report (NSF Form 98A); however, submission of the requested information is not mandatory and is not a precondition of future awards. If you do not wish to submit this information, please check this box ☐

Please enter the numbers of individuals supported under this NSF grant.
Do not enter information for individuals working less than 40 hours in any calendar year.

*U.S. Citizens/ Permanent Visa	PI's/PD's		Post-doctorals		Graduate Students		Under-graduates		Precollege Teachers		Others	
	Male	Fem.	Male	Fem.	Male	Fem.	Male	Fem.	Male	Fem.	Male	Fem.
American Indian or Alaskan Native					5			1				
Asian or Pacific Islander												
Black, Not of Hispanic Origin												
Hispanic												
White, Not of Hispanic Origin												
Total U.S. Citizens					5			1				
Non U.S. Citizens												
Total U.S. & Non-U.S. ..					5			1				
Number of individuals who have a handicap that limits a major life activity.												

*Use the category that best describes person's ethnic/racial status. (If more than one category applies, use the one category that most closely reflects the person's recognition in the community.)

AMERICAN INDIAN OR ALASKAN NATIVE: A person having origins in any of the original peoples of North America, and who maintains cultural identification through tribal affiliation or community recognition.

ASIAN OR PACIFIC ISLANDER: A person having origins in any of the original peoples of the Far East, Southeast Asia, the Indian subcontinent, or the Pacific Islands. This area includes, for example, China, India, Japan, Korea, the Philippine Islands and Samoa.

BLACK, NOT OF HISPANIC ORIGIN: A person having origins in any of the black racial groups of Africa.

HISPANIC: A person of Mexican, Puerto Rican, Cuban, Central or South American or other Spanish culture or origin, regardless of race.

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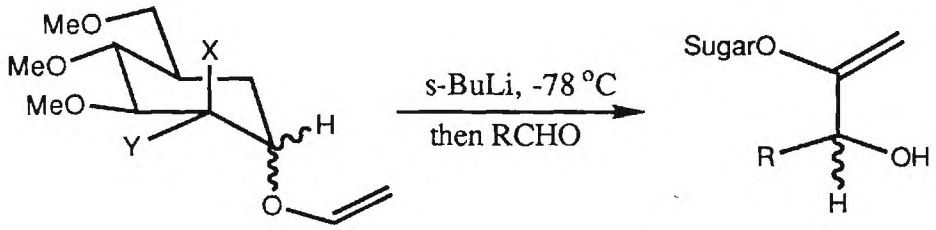
THIS PART WILL BE PHYSICALLY SEPARATED FROM THE FINAL PROJECT REPORT AND USED AS A COMPUTER SOURCE DOCUMENT. DO NOT DUPLICATE IT ON THE REVERSE OF ANY OTHER PART OF THE FINAL REPORT.

Final Technical Report
NSF Grant **CHE-8612735**

Principal Investigator: **Patrick G. McDougal**
School of Chemistry
Georgia Institute of Technology
Atlanta, GA 30332

A. Directed Lithiations of Enol Ethers: Chiral Series

We have extended our directed lithiation of enol ethers (see Section C, refs 1 and 5) into a series of chiral nonracemic derivatives derived from carbohydrates. A survey of the sugar auxillaries used are shown in Scheme 1. Alpha lithiation of the enol ethers followed by alkylation with benzaldehyde produced the mixture of diastereomers shown in Scheme 1. The α-D-mannose derivative **3** proved to be the most efficacious and hence this derivative was reacted with a representative array of aldehydes. Scheme 1 shows that the diastereoselectivity is highly dependent on the nature of the aldehyde and the sense of the selectivity actually changes in proceeding from n-hexanal (**7***S*/*R* 65:35) to pivaldehyde (**8***S*/*R* 23:77).

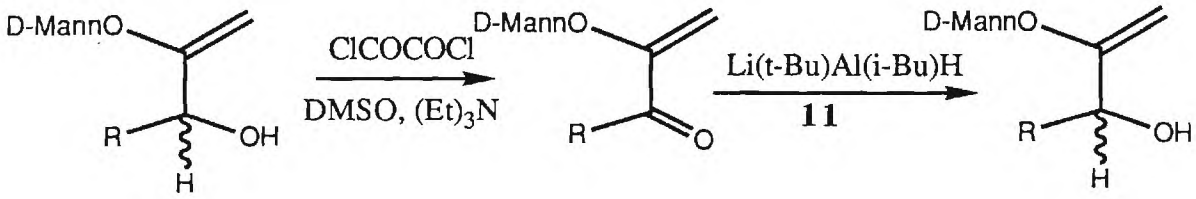


1 X=H; Y=OMe; β-anomer → 4 R=Ph	*S*/*R* ~50:50
2 X=H; Y=OMe; α-anomer → **5** R=Ph	*S*/*R* 77:23
3 X=OMe; Y=H; α-anomer → **6** R=Ph	*S*/*R* 93:7
3 X=OMe; Y=H; α-anomer → **7** R=n-pentyl	*S*/*R* 65:35
3 X=OMe; Y=H; α-anomer → **8** R=i-Pr	*S*/*R* 55:45
3 X=OMe; Y=H; α-anomer → **9** R=t-Bu	*S*/*R* 23:77

Scheme 1

As the selectivity was mediocre for the aliphatic aldehydes an alternate pathway for the production of chiral alcohols **7-9** was

explored. As shown in Scheme 2, this involved oxidation of the alcohol to a ketone followed by reduction to a new mixture of alcohols. From a survey of various reducing agents it was determined that bulky hydride reducing agents such as L-selectride and the aluminate **11** (see Scheme 2) gave the highest diastereoselectivity. Since the desired alcohols **7-9** were difficult to liberate from the intermediate borate formed in the L-selectride reaction the aluminate**11** proved to be the superior reagent The diastereoselectivity for this process was much improved relative to that shown in Scheme 1. Hence it is now possible to acheive high selectivity in both the aliphatic or aromatic systems.

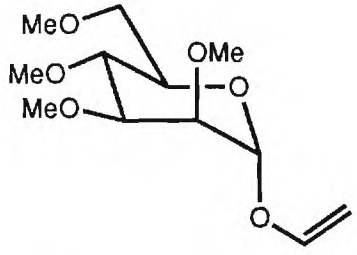


7 R=n-pentyl
8 R=i-Pr
9 R=t-Bu

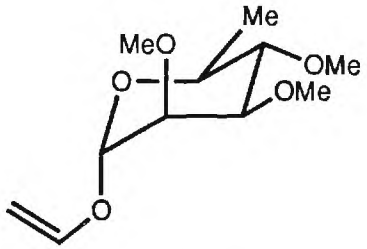
7 *S/R* 9:91
8 *S/R* 5:95
9 *S/R* 3:97

Scheme 2

One of the potential disadvantages in utilizing carbohydrates as chiral auxillaries is the fact that usually only one enantiomer is readily available. For example with mannose the L-enantiomer is about 100 times more expensive than the D-enantiomer. For our purposes we have found that L-rhamnose (~ 3 times more expensive than D-mannose) is the functional equivalent of L-mannose. Hence the permethylated rhamnose derivative **10** performs all the same chemistry as described above for the mannose derived enol ether **3** with virtually the identical selectivity.

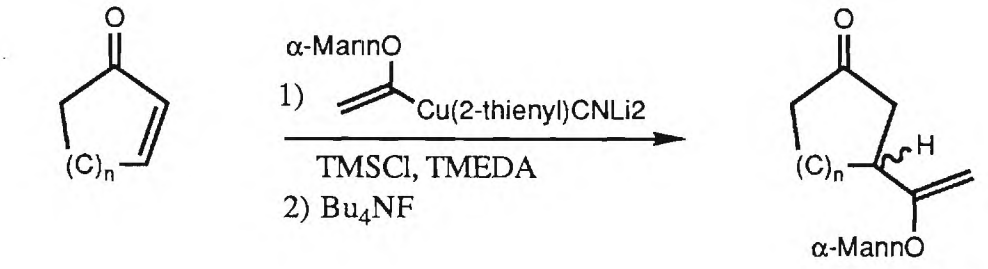


3 D-Mannose Derivative

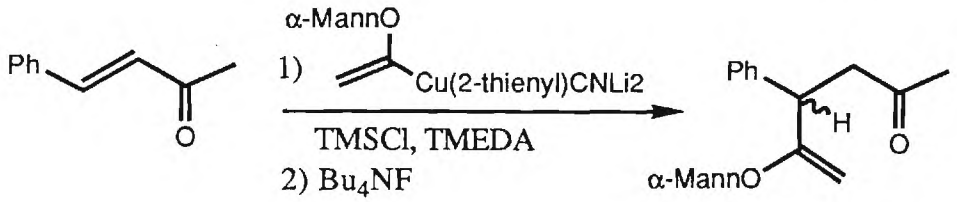


10 L-Rhamnose Derivative

In addition to the simple 1,2-additions of the chiral enol ethers to aldehydes, we have also investigated the conjugate addition reactions as illustrated in Scheme 3. Initially we had problems finding a cuprate reagent which would yield the conjugate addition product. We ultimately found that the higher order cuprate reagent formed via the lithium 2-thienylcyanocuprate gave the best yields of conjugate addition. The stereoselectivity varied from 2:1 for cyclopentenone to 10:1 for cycloheptenone. The stereoselectivity for acyclic enones is also an impressive 10:1, although in this instance the sense of the stereoselectivity has not yet been determined.



n=1 *R/S* 2:1
n=2 *R/S* 5:1
n=3 *R/S* 10:1



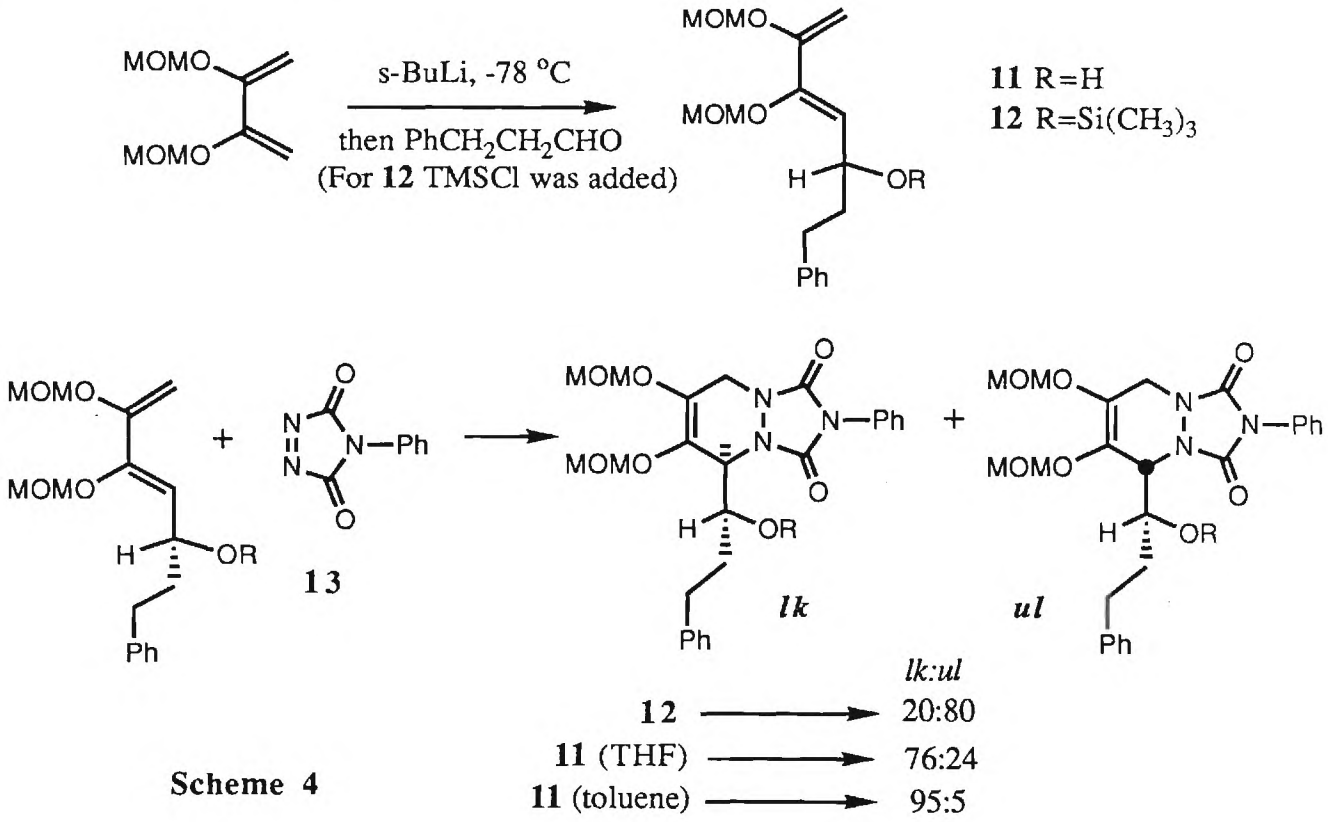
10:1 (stereochemistry unassigned)

Scheme 3

B. Asymmetric Diels-Alder Reactions:

Two new asymmetric dienes have been prepared and studied for their stereoselectivity in the Diels-Alder reaction. The first (see Scheme 4) is a derivative of our previous work on dienes bearing a chiral allylic center (see Section C, ref 4). The chiral dienes **11** and **12** were prepared via our β-lithiation technology. (see ref #, Section C). The cycloaddition of the protected derivative **12** with the triazalone **13** yielded an 80:20 mixture of products. As is usual with

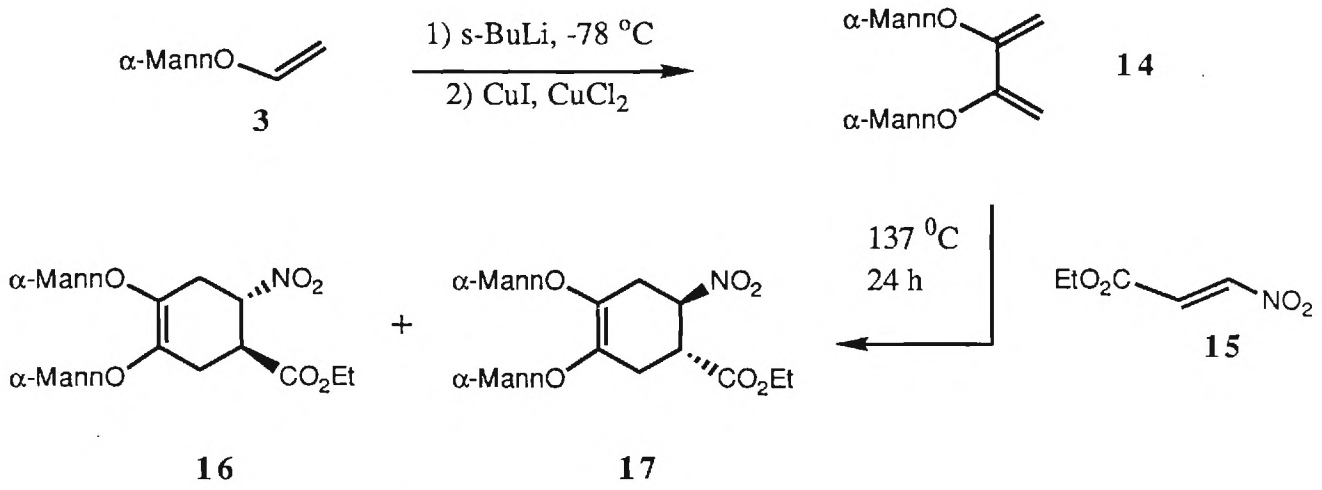
the aza dienophiles the *ul* stereoisomer was predominant. The more interesting result was that free alcohol **11** yielded the *lk* stereoisomer. The solvent dependence and the sense of the



Scheme 4

stereoselectivity indicates that a hydrogen bonding between the dienophile and diene is taking place during the transition state. The hydroxy diene **11** reacts with both N-phenylmaleimide and benzoquinone with the same *lk* stereoselectivity, although high pressure (6.5 kbar) is necessary to achieve cycloaddititon in these cases.

Finally the C-2 symmetric chiral nonracemic diene **14** (see Scheme 5) was synthesized via the dimerization of enol ether **3**. As is typical with 2,3-dialkoxy dienes, **19** was not particularly reactive in the Diels-Alder reaction. It did react with the nitrostyrene **15** to yield the expected Diels-Alder adducts **16** and **17.** The reaction produces an 85:15 mixture of diastereomers but as of yet we have not been able to determine which is the major isomer.



Scheme 5

C. Publications Acknowleding NSF Grant (Full Granting Period):

1. McDougal, P. G.; Rico, J. G.; Stereoselective Synthesis and α-Metallation of 1-Alkoxy Polyenes. *J. Org. Chem.* **1987**, *52*, 4817-4819.

2. McDougal, P. G.; Condon, B. D.; Laffossee, M. D., Jr.; Lauro, A. M.; VanDerveer, D.: Diastereoselective Reactions of an Acyclic α-Lithiated Sulfide: A Case of Thermodynamic Control. *Tetrahedron Letters* **1988**, *29*, 2547-2550.

3. McDougal, P. G.; Condon, B. D.: Retention of Configuration in the Desilylative Hydroxyalkylation of α-Silyl Sulfides. *Tetrahedron Letters* **1989**, *30*, 789-793.

4. McDougal, P. G.; Jump, J. M.; Rojas, C. M.; Rico, J. G.: Diels-Alder Reaction of Asymmetric Alkoxy Dienes: Oxygen Versus Sulfur as an Allylic Directing Group. *Tetrahedron Letters* **1989**, *30*, 3897-3901.

5. McDougal, P. G.; Rico, J. G.; Condon, B. D.; Kerrigan, J. E.: Direct β-Lithiation of Methoxymethyl Enol Ethers. *J. Org. Chem.* **1991**, accepted for publication.

6. McDougal, P. G.; Dicesare, J.; Starks, L. J.; Culligan, P.: Chiral Acyl Anion Equivalents Based on Carbohydrate Derived Enol Ethers, in preparation.

D. Data on Scientific Collaborators:

Joseph G. Rico, graduate student, Ph.D. June, 1987, presently Research Scientist, Monsanto.

Brian D. Condon, graduate student, Ph.D. October, 1989, presently Research Scientist, Vista Chemical Co.

Joseph M. Jump, graduate student, Ph.D. December, 1990, presently Research Scientist, Research Triangle Institute.

John Dicesare, presently graduate student.

John Kerrigan, presently graduate student.

STEREOSELECTIVE BOND FORMATION
via
LITHIATION OF ASYMMETRIC ACYCLIC SULFIDES

A THESIS
Presented to
The Faculty of the Division of Graduate Studies

by

Brian D. Condon

In Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy in Chemistry

Georgia Institute of Technology
October 1989

Abstract

Directed Lithiations of Enol Ethers: Stereoselective Synthesis and Reactions of Substituted Enol Ethers

Joseph G. Rico

Page 145

Directed by Dr. Patrick G. McDougal

The directive effect of the methoxymethyl (MOM) group in the deprotonation of vinyl ethers was studied. We discovered that methoxymethyl vinyl ethers can undergo β-lithiation by simple deprotonation. This discovery inspired us to synthesize a wide variety of methoxymethyl enol ethers in order to study the potential of the β-lithiation. During this study we found that 2-methoxymethyl dienol ethers were some of the best substrates for the β-lithiation and conclude that the β-lithiation of methoxymethyl vinyl ethers is indeed a new general reaction.

In an effort to synthesize substrates for β-lithiation, we found that the MOM group facilitates the α-lithiation of enol ethers as well. We then directed our attention to the α-lithiation of 1-methoxymethyl polyenes. A general strategy was developed to synthesize these 1-alkoxypolyenes. The requisite cis-allylic ethers prepared by reduction of substituted methoxymethyl propargylic ethers with H_2 on poisoned palladium catalyst. The cis-allylic ethers are subjected to 1,4-elimination using lithium diisopropyl amide (LDA) to

give 1**E**,3**E**-4-substituted-1-alkoxy dienes and 1**E**,3**E**,5**E**-6-substituted-1-alkoxy trienes in good overall yield. 1-Methoxymethoxy dienes are smoothly deprotonated α to oxygen when treated with s-butyllithium at -78°C. For successful α-deprotonation of the trienyl system it was necessary to switch the base to n-butyllithium and the solvent to dimethoxy ethane in the presence of TMEDA. Most importantly, the methoxylmethyl group is necessary for the successful deprotonation of the 1-alkoxytrienes, as 1**E**,3**E**,5**E**-1-methoxy-6-methyl-1,3,5-hexatriene did not metallate under these conditions.

The reaction of the β-lithiation product from 3**E**-2-methoxymethoxy-4-isopropyl-1,4-butadiene with acetaldehyde followed by silylation yielded a diene which underwent a face selective Diels-Alder reaction with N-phenylmaleimide. The stereochemistry of this adduct was confirmed by an X-ray crystal structure. In addition 1E,3**E**-1-alkoxy-5-dimethyl-t-butylsiloxy-1,3-hexadiene also underwent a face selective Diels-Alder reaction with N-phenylmaleimide. The nature of the face selectivity in this case is presumed to be the same as that observed for the previous diene.

SUMMARY

Deprotonation of 2-(1'-methyl-2'-phenylthioethyl)-1,3-dioxolane with s-butyllithium followed by reaction with benzaldehyde produces 2-(1'-methyl-2'-phenylthio-3-hydroxy-3-phenylpropyl)-1,3-dioxolane as an 80:20 mixture of two diastereomers. Although four diastereomers could have been produced in this reaction only two were observed. The work in this thesis was directed toward unraveling the factors which contribute to the stereoselectivity observed in the above reaction.

Deprotonation of the above sulfide occurs α to the sulfur atom and renders the lithiated carbon chiral. When the anion is quenched with trimethylsilyl chloride a 98:2 ratio of diastereomers was produced. An x-ray crystal of a closely related derivative showed that the stereochemistry of the major isomer was anti. Through a series of experiments it was shown that this α-lithiated sulfide was configurationally labile even at -78°C and reacts preferentially via the anti isomer. The key observation here was that both the syn and anti isomers of 2-(1'-methyl- 2'-phenylthio- 2'-tributylstannylethyl)-1,3-dioxolane yielded the same 98:2 ratio of anti/syn diastereomers when subjected to Sn/Li exchange followed by quenching with trimethylsilylchloride. The large preference for the anti isomer explains the absence of two diastereomers when benzaldehyde was used to quench the

reaction.

Reaction of the lithiated sulfide with prochiral electrophiles, such as benzaldehyde, produces an additional chiral center. As mentioned above this center is produced as a 4:1 mixture of stereoisomers when benzaldehyde was used as the aldehyde. When α,ß-unsaturated aldehydes were utilized in this reaction the stereoselectivity droped noticeably. For example crotonaldehyde gave a 1:1 ratio and methacrolein gave a 2:1 ratio of diastereomers. However when α-bromocrotonaldehyde was used in this reaction the selectivity (9:1) was even better than benzaldehyde. The selectivity was studied as a function of solvent and in general both non-polar mediums (pentane) and complexing agents (HMPA) decreased the overall selectivity relative to THF. A model, first proposed by McGarvey, was used to rationalize the observed selectivity. A critical factor in all our rationalizations of stereoselectivity is internal coordination of the lithium atom to the oxygens of the dioxolane ring.

The above observations were extended into a number of related systems. In particular the phenylthio group in the parent sulfide was replaced by o-methoxyphenylthio and o-t-butylphenylthio. The same general trends were observed with these systems with one exception. When the α-lithiated o-methoxyphenyl sulfide derivative was formed

in pentane and reacted with benzaldehyde in the same medium a dramatic decrease in selectivity was observed. In this case we believe competing internal coordination between the dioxolane oxygens and the phenolic oxygen lead to a decrease in selectivity.

Finally the stereochemistry of reductive desilylative hydroxyalkylation was studied. The procedure outlined above allowed for the preparation of anti-2-(1'-methyl-2'-phenylthio-2'-trimethylsilylethyl)- 1,3-dioxolane. The corresponding syn isomer, as a 3:1 mixture of diastereomers, was prepared from the anti isomer by reductive desulfenylation followed by quenching with trimethylsilyl chloride. Independent treatment of the syn and anti isomers with tetrabutylammonium fluoride in the presence of benzaldehyde produced hydroxyalkylated products with the same syn and anti stereochemistry respectively. Hence the C-Si bond is transformed into a C-C bond with retention of configuration.

SYNTHESIS AND USE OF CHIRAL DIENES IN THE ASYMMETRIC DIELS-ALDER REACTION

A THESIS
Presented to
The Faculty of the Division of Graduate Studies

by

Joseph M. Jump

In Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy in Chemistry

Georgia Institute of Technology
December 1990

SUMMARY

Due to the high degree of stereoselectivity inherent to the Diels-Alder reaction there is presently much interest in trying to delineate the factors that govern facial selectivity when asymmetric dienes are utilized in order to achieve high asymmetric induction. This thesis reports on the stereoselective synthesis of three asymmetric, 1-alkoxy substituted, acyclic 1E, 3E dienes which bear an asymmetric center at the allylic position. In each of these three cases, a general four step procedure starting from chiral, non-racemic precursors was utilized where the last step to exclusively form the desired 1E, 3E diene involved a cis-1,4-elimination of the elements of methanol from a Z-1,4-dialkoxy substituted butenyl system using a lithium amide base. The asymmetric center of these novel dienes are substituted with a heteroatom (oxygen or sulfur), an alkyl group, and a hydrogen atom. It was determined that when the heteroatom was oxygen, the asymmetric diene was synthesized in enantiomerically pure form but in the dienyl system where the heteroatom was sulfur, extensive racemization of the stereocenter had occurred. The facial selectivity of these dienes was probed using three dienophiles: N-phenylmaleimide (NPM), 1,4-benzoquinone, and 4 - phenyl - 1,2,4 - triazoline - 1,3 - dione (PTAD). One general trend observed was that *like* facial selectivity was preferred in the cases where the heteroatom bore an oxygen substituent but this selectivity diminished upon switching to sulfur for all three dienophiles. This is consistent with the results of Fallis et. al., but not as dramatic. Another trend observed was that facial selectivity was dependent on the dienophile used with NPM being more *like* selective than benzoquinone which, in turn, is more *like* selective than PTAD. A final trend observed was that substituents at the C-1 position can effect facial selectivity and the conclusion made was that electron donors via resonance increase *like* facial

selectivity. The model used to describe facial selectivity in these systems is that proposed by Cieplak where the best σ-donor bound to the asymmetric center prefers to orient itself perpendicular to the plane of the dienyl system in order to donate electron density into the antiperiplanar incipient bond associated with the transition state. Two other acyclic dienyl systems synthesized were derivatives of α-D-mannose. The synthetic route to our first carbohydrate-derived diene paralleled that used for the asymmetric dienes mentioned earlier but the sugar moiety was to be incorporated at C-1 of the dienyl system. It was found that following the normal elimination step, a mixture of three geometrically isomeric dienes had formed perhaps because of a chelation and / or an isomerization mechanism. The facial selectivity offered by the desired E,E isomer in its reaction with NPM was poor (60 : 40). The second diene, synthesized via a divinyl cuprate coupling reaction, posessed mannose substituents at the C-2 and C-3 positions and therefor had a C_2 axis of symmetry. This dienyl system, due to the large steric demand of the bulky sugar groups in the requisite s-cis conformation, failed to react with dimethyl fumarate or two other dienophiles which were derivatives of benzoquinone under a variety of reaction conditions. It did, however, react smoothly with the more activated dienophile, trans-ethyl-2-nitroacrylate, to yield an 85 : 15 mixture of diastereomers. Attempts at proving the stereochemistry of the adducts were made but this goal had not been reached.